USSN 09/890,335
Supplemental Amendment filed July 14, 2009

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Remarks/Arguments

No new matter is believed to be added by this Amendment.

The amendment to the chemical structure occurring in the paragraph spanning page 15 line 4 to page 16 line 2 is to correct a typographical error occurring within the phosphate group of the pictured chemical structure. Specifically, an oxygen atom is included with the phosphate group pictured as bound to group R_3, so that "P-R_3" is now "P-O-R_3". Support for this amendment is provided in the attached Appendix. While one skilled in the art may presume the presence of the oxygen atom in the structure as currently presented (see for instance a similar representation and typographical error in Mathew-van Holde's Biochemistry p. 303; Appendix), as Applicant is aware of the typographical error, Applicant corrects the error herein. This correction is also supported for instance by the disclosure at pages 15-16 that the chemical structure relates to the class of phospholipids having the formula defined therein, as phospholipids typically include the inserted oxygen. See for instance the Appendix included herein.

In the event that the Examiner has any questions or concerns regarding this application, the Examiner is invited to contact the below-signed representative by telephone to discuss.

Respectfully submitted,

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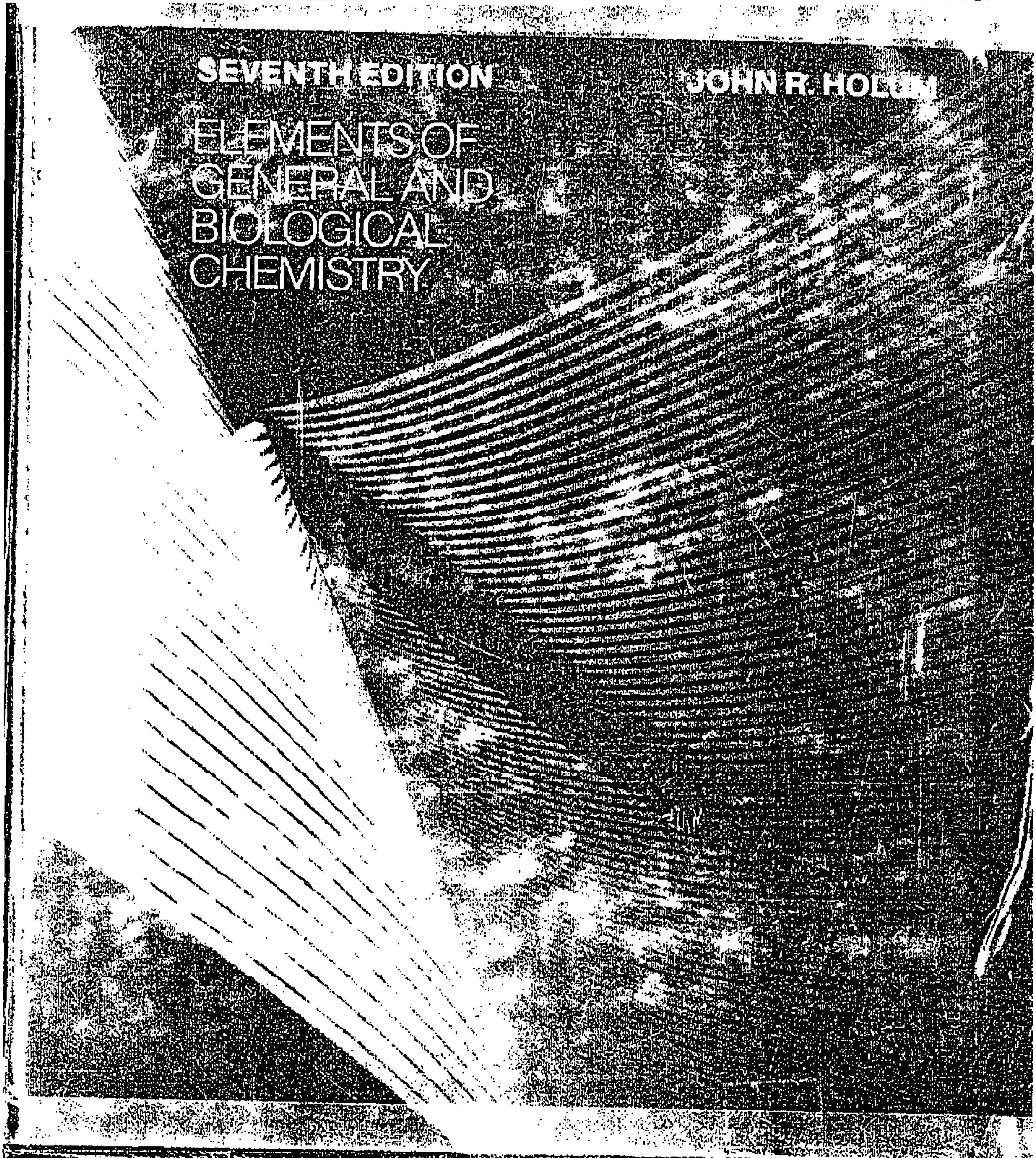
Appendix

Holum, Elements of General and Biological Chemistry: John Wiley & Sons, USA (1987) – pages 324, 325.

Stryer, Biochemistry: W.H. Freeman and Company, San Francisco, California (1981) – pages 208, 209.

Mathews and van Holde, Biochemistry: The Benjamin/Cummings Publishing Company, Redwood City, California (1990) – pages 303, 304.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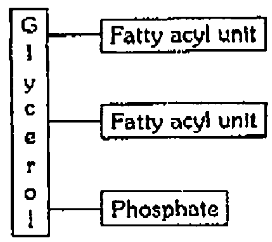
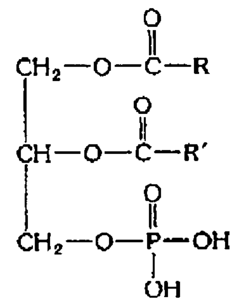
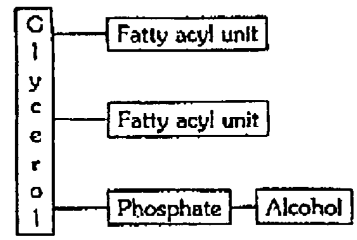
joined by a phosphate ester link to a small alcohol molecule. When this link is absent, the material is called phosphatidic acid.



Components of phosphatidic acid



Phosphatidic acid



Components of phosphoglycerides

Cephalin is from the Greek *kephale*, head. Cephalin is found in brain tissue.

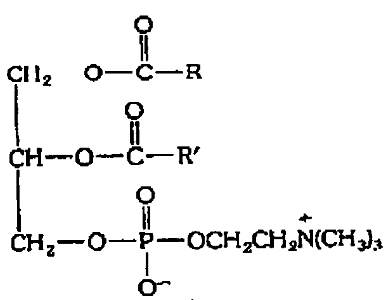
The three principal phosphoglycerides are esters that are formed between phosphatidic acid and either choline, ethanolamine, or serine to give, respectively, phosphatidylcholine (lecithin), **2**, phosphatidylethanolamine (cephalin), **3**, and phosphatidylserine, **4**.

$HOCH_2CH_2\overset{+}{N}(CH_3)_3$ — Choline (a cation)

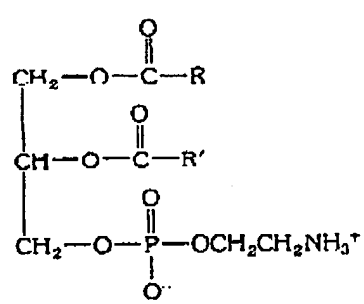
$HOCH_2CH_2NH_2$ — Ethanolamine

$HOCH_2CH(NH_3^+)CO_2^-$ — Serine

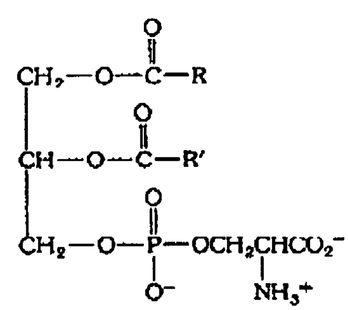
As the structures of **2**, **3**, and **4** show, one part of each phosphoglyceride molecule is very polar because it carries full electrical charges. The remainder is nonpolar and hydrocarbon-like. These characteristics have important implications in understanding how phosphoglycerides are used to make cell membranes (Section 15.5).



2
Phosphatidylcholine (lecithin)



3
Phosphatidylethanolamine (cephalin)

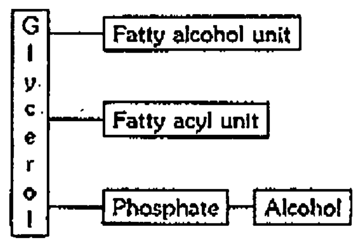


4
Phosphatidylserine

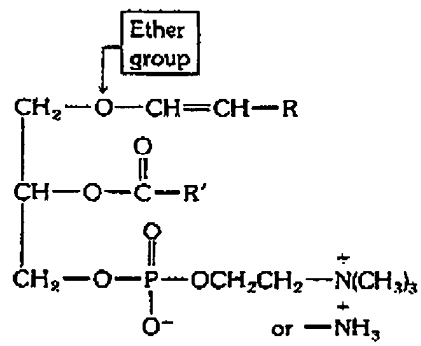
Lecithin is from the Greek *lekitos*, egg yolk—a rich source of this phospholipid.

When pure, lecithin is a clear, waxy solid that is very hygroscopic. In air, it is quickly attacked by oxygen, which makes it turn brown in a few minutes. Lecithin is a powerful emulsifying agent for triacylglycerols, and this is why egg yolks, which contain it, are used to make the emulsions found in mayonnaise, ice cream, custards, and cake dough.

Plasmalogens. The **plasmalogens** make up another family of glycerol-based phospholipids, and they occur widely in the membranes of nerve cells and muscle cells. They differ from the other phosphoglycerides by the presence of an unsaturated ether group instead of an acyl group at one end of the glycerol unit.



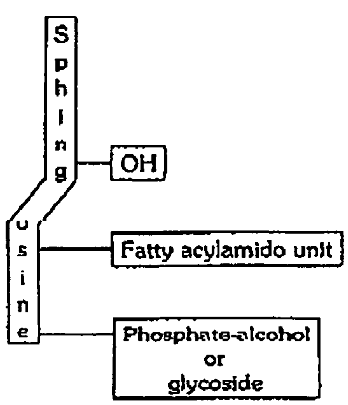
Components of plasmalogens



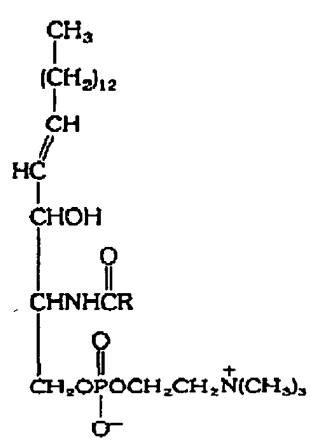
Plasmalogens

Sphingolipids. The two types of sphingosine-based lipids or **sphingolipids** are the sphingomyelins and the cerebrosides, and they are also important constituents of cell membranes. The sphingomyelins are phosphate diesters involving sphingosine. Their acyl units occur as acylamido parts, and they come from unusual fatty acids that are not found in neutral fats.

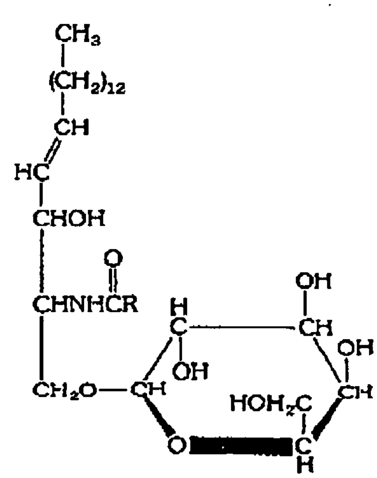
The cerebrosides are not actually phospholipids. Instead they are **glycolipids**, lipids with a sugar (i.e., glycose) unit and not a phosphate ester system. The sugar unit is usually that of D-galactose, or D-glucose, or amino derivatives of these.



Components of sphingolipids



Sphingomyelins



Cerebrosides

Second Edition

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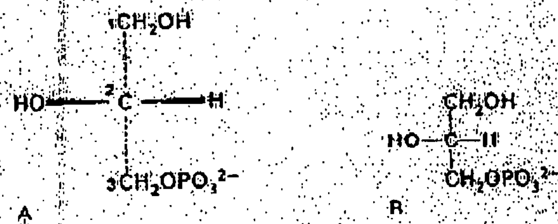
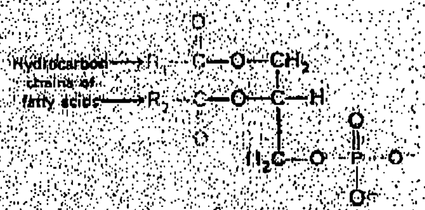


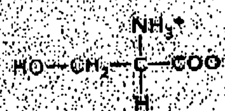
Figure 10-4
Absolute configuration of the glycerol 3-phosphate moiety of membrane lipids: (A) H and OH, attached to C-2, are in front of the plane of the page, whereas C-1 and C-3 are behind it. (B) Fischer representation of this structure. In a Fischer projection, horizontal bonds denote bonds in front, whereas vertical bonds denote bonds behind the plane of the page.



Phosphatidate
(Diacylglycerol 3-phosphate)

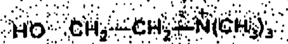
In phosphoglycerides, the hydroxyl groups at C-1 and C-2 of glycerol are esterified to the carboxyl groups of two fatty acid chains. The C-3 hydroxyl group of the glycerol backbone is esterified to phosphoric acid. The resulting compound, called *phosphatidate* (or diacylglycerol-3-phosphate), is the simplest phosphoglyceride. Only small amounts of phosphatidate are present in membranes. However, it is a key intermediate in the biosynthesis of the other phosphoglycerides.

The major phosphoglycerides are derivatives of phosphatidate. The phosphate group of phosphatidate becomes esterified to the hydroxyl group of one of several alcohols. The common alcohol moieties of phosphoglycerides are serine, ethanolamine, choline, glycerol, and inositol.

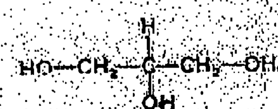


Serine

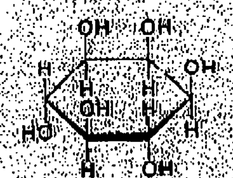
Ethanolamine



Choline

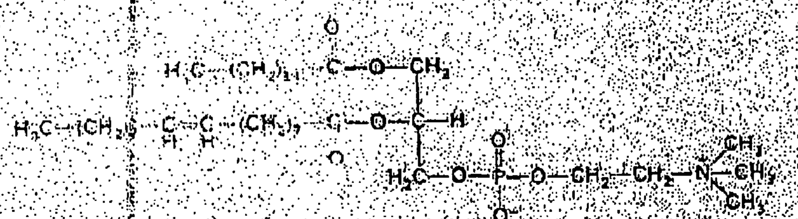


Glycerol



Inositol

Now let us link some of these components to form phosphatidyl choline, a phosphoglyceride found in most membranes of higher organisms.



A phosphatidyl choline
(1-Palmitoyl-2-oleoyl-phosphatidyl choline)

The structural formulas of the other principal phosphoglycerides—namely, phosphatidyl ethanolamine, phosphatidyl serine, phosphatidyl inositol, and diphosphatidyl glycerol—are given in Figure 10-5.

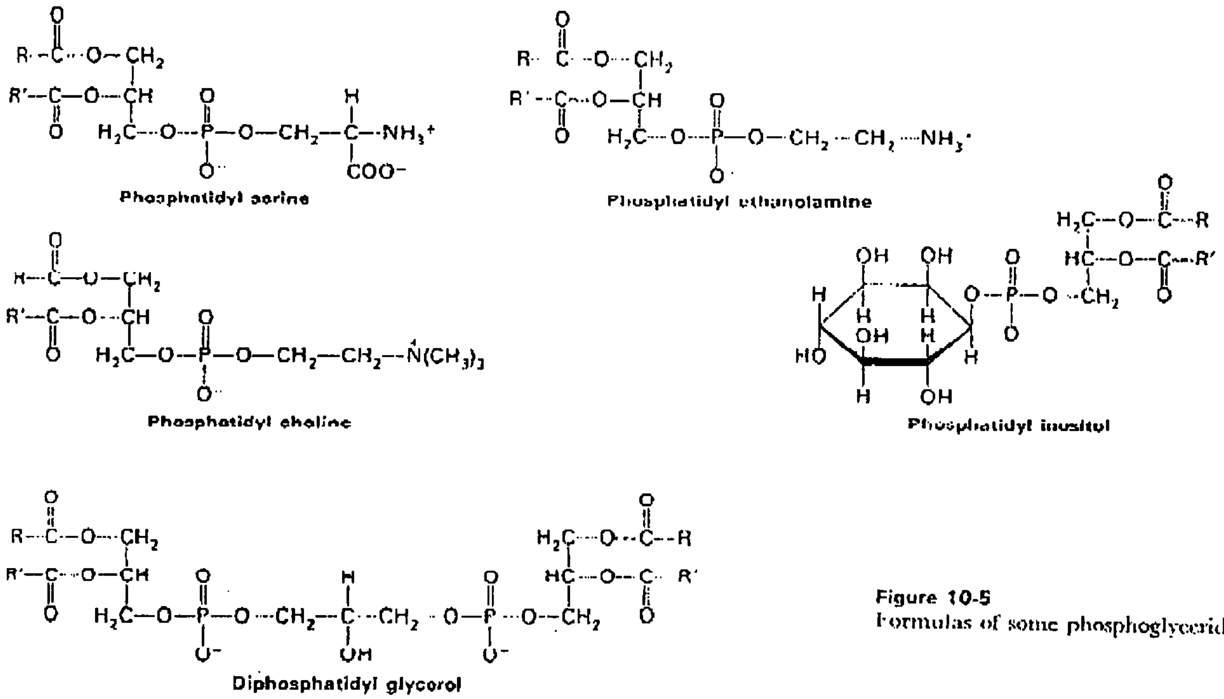
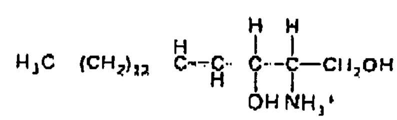
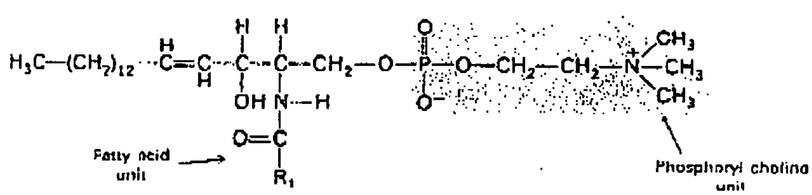


Figure 10-5
Formulas of some phosphoglycerides.

Sphingomyelin is the only phospholipid in membranes that is not derived from glycerol. Instead, the backbone in sphingomyelin is *sphingosine*, an amino alcohol that contains a long, unsaturated hydrocarbon chain. In sphingomyelin, the amino group of the sphingosine backbone is linked to a fatty acid by an amide bond. In addition, the primary hydroxyl group of sphingosine is esterified to phosphoryl choline. As will be shown shortly, the conformation of sphingomyelin resembles that of phosphatidyl choline.



Sphingosine



Sphingomyelin

BIOCHEMISTRY

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Illustration concepts by Audre W. Newman
with art contributions from Irving Geis

Cover

Dimer of *trp* repressor protein, with bound tryptophan in blue. The protein binds to DNA and regulates expression of the *trp* genes that control tryptophan biosynthesis. Crystal structure by Paul Sigler et al.; image by Jane and David Richardson.

Frontispiece

Figure 11.15a The T state of aspartate transcarbamoylase, as determined by x-ray diffraction.

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The Lipid Constituents of Biological Membranes

All biological membranes contain lipids as major constituents. The molecules that play the dominant roles in membrane formation all have highly polar head groups and, in most cases, *two* hydrocarbon tails. There is a molecular sense to this: If a large head group is attached to a single hydrocarbon chain, the molecule is wedge shaped and will tend to form spherical micelles (Figure 9.5a). A double tail yields a roughly cylindrical molecule, which can easily pack in parallel to form extended sheets of membranes. As indicated in Figure 9.5b, such membranes will be bilayers, with the hydrophilic head groups facing outward into the aqueous regions on either side. A number of classes of membrane-forming lipids share this type of structure; they differ principally in the nature of the head group. We shall describe a few examples of each.

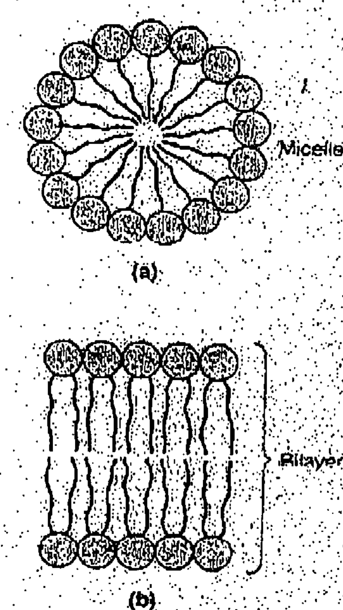

Figure 9.5
How molecular shape of lipids determines the structures they form. (a) The single tail of a fatty acid makes the molecule wedge-shaped, favoring micelle formation. (b) The multiple tails on membrane-forming lipids make the molecules more cylindrical, so that planar bilayer sheets can be formed.

Glycerophospholipids

Glycerophospholipids (also called phosphoglycerides) are the major class of naturally occurring phospholipids, lipids with phosphate-containing head groups. These compounds make up a significant fraction of the membrane lipids throughout the bacterial, plant, and animal kingdoms. All can be considered to be derivatives of glycerol-3-phosphate. Carbon 2 in glycerol-3-phosphate is a chiral center, and the naturally occurring glycerophospholipids are derivatives of the L enantiomer. The general structure of this group of compounds is shown in Figure 9.6. In panel (a) is depicted the stereochemical configuration. Panel (b) shows the molecule in the manner we will generally use to represent membrane lipids, with the hydrophobic tails drawn to the right and the hydrophilic head group to the left. Usually, R_1 and R_2 are acyl side chains derived from the fatty acids; often one is saturated, the other unsaturated. The R_3 group varies greatly, and it is this that confers the greatest variation in properties among the glycerophos-

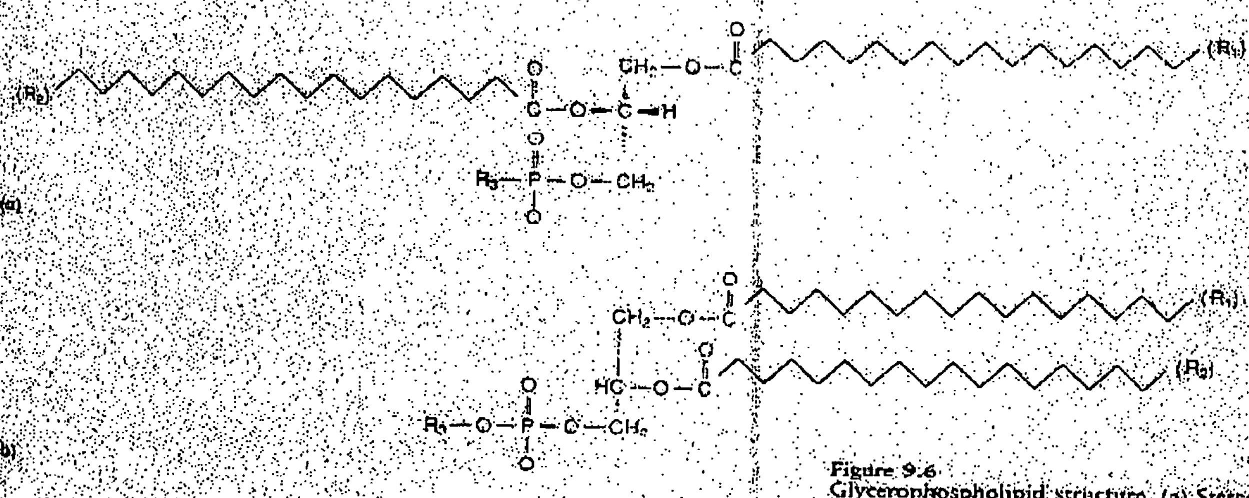

Figure 9.6
Glycerophospholipid structure. (a) Stereochemical view of L-enantiomer. (b) A conventional visualization.

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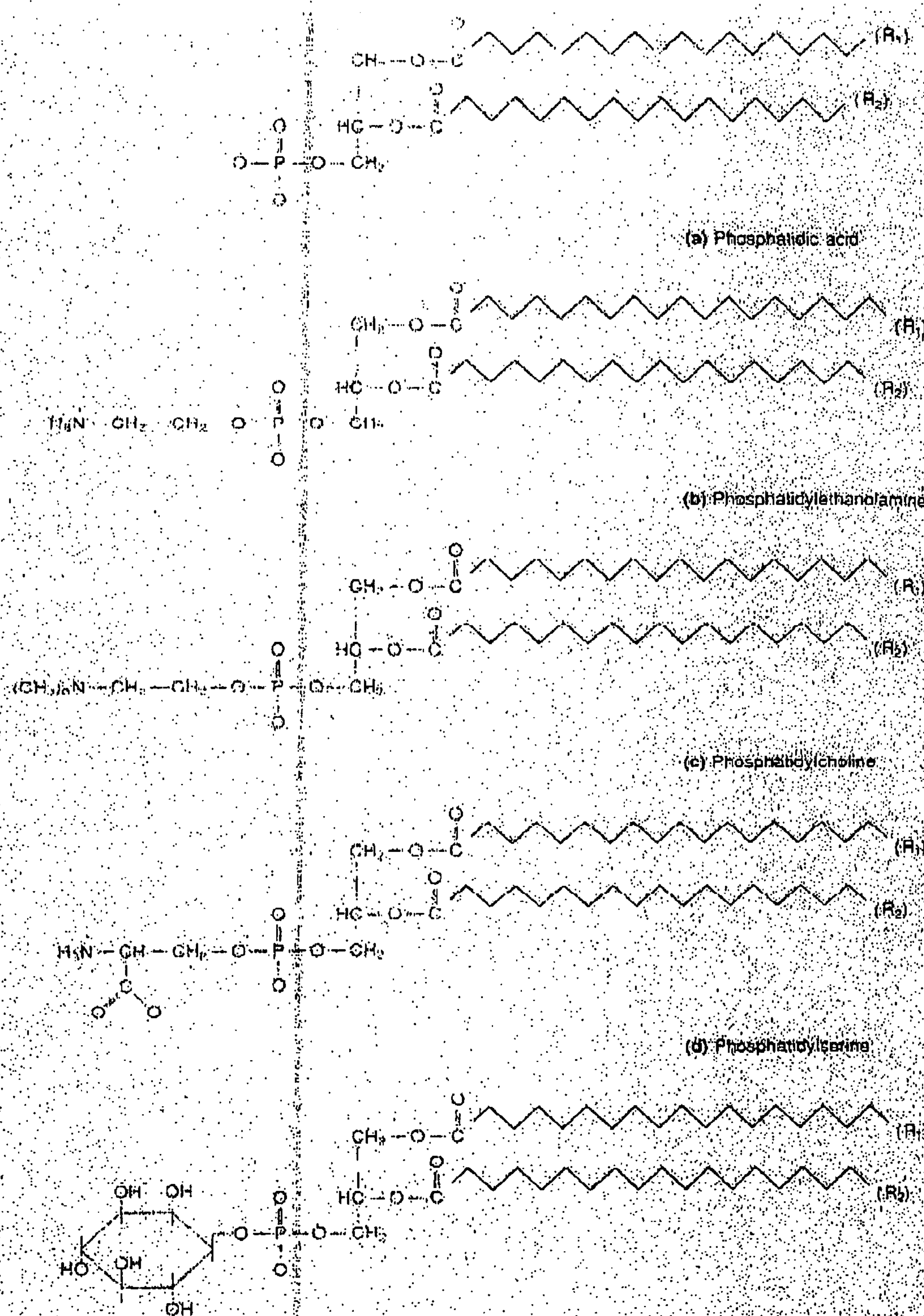

Figure 9.7
Examples of common glycerophospholipids. The hydrophobic R groups are indicated in yellow, the glyceryl moiety in black, and the very hydrophilic head groups in blue. All may be considered derivatives of phosphatidic acid (a).